

The University of Chicago

STUDIES ON
HEMOCONCENTRATION AND
SHOCK FOLLOWING SEVERE
HEMORRHAGE

A PART OF A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
DECEMBER, 1942

By
RAYMOND E. WESTON

Reprinted from
THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 138, No. 3, February, 1943

The University of Chicago

STUDIES ON
HEMOCONCENTRATION AND
SHOCK FOLLOWING SEVERE
HEMORRHAGE

A PART OF A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
DECEMBER, 1942

By
RAYMOND E. WESTON

Reprinted from
THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 138, No. 3, February, 1943



STUDIES ON HEMOCONCENTRATION AND SHOCK FOLLOWING SEVERE HEMORRHAGE¹

RAYMOND E. WESTON

From the Department of Physiology of the University of Chicago, Chicago, Ill.

Received for publication September 17, 1942

Whether severe hemorrhage can lead to true shock is still controversial, as the recent literature reveals. If the reduction in blood volume which follows severe hemorrhage fails to produce shock, the theory which attributes the development of traumatic shock to oligemia, resulting from local fluid loss at the site of injury, would be weakened considerably. The work presented here may contribute to the clarification of this problem by demonstrating that shock, with its characteristic manifestations as set forth by Moon, can follow hemorrhage under certain experimental conditions.

Some investigators (Moon; Coonse *et al.*; Mahaffey)² have reported that hemodilution invariably follows hemorrhage and have used this observation as the basis for a differentiation between the effects of hemorrhage and shock, emphasizing that, after hemorrhage, hemoconcentration may occur only terminally. More recently, Moon (1) again has stressed that, despite similarities, hemorrhage and shock should be differentiated, clinically and experimentally, lest erroneous conclusions be drawn. Price (2) concurred that in normal anesthetized dogs severe hemorrhage always produces hemodilution and that the outstanding physiologic and pathologic effects of acute hemorrhage are not found in shock produced by other means.

Others (Blalock; Freeman; Davis)² have contended that after severe hemorrhage all of the postulated signs of shock, including hemoconcentration, may develop. Blalock (3) and Harkins (4), in their recent reviews, conclude that the differentiation of hemorrhagic from other types of shock is unsound, and that the sequelae of post-hemorrhagic oligemia may include hemoconcentration, if sufficient time is allowed to elapse before death or therapy.

In the light of Starling's theory of fluid exchange in the capillary bed, some hemodilution must necessarily occur after hemorrhage, due to the shift of body water into intravascular circulation as the capillary hydrostatic pressure falls. In well hydrated animals, the early hemodilution following hemorrhage is so great that it can either compensate for extensive blood loss or else (partially or totally) mask subsequent hemoconcentration. It was felt that if the effects of such hemodilution were reduced by deprivation of water, hemoconcentration might be demonstrated to occur after graded bleeding, a procedure by which the fluid reserves of the body are known to be depleted severely (5).

¹ Supported by a grant from The Michael Reese Research Foundation.

² All references without index numbers can be found in reviews 3 and 4.

METHODS. Twenty-six healthy, adult, unanesthetized mongrel dogs, weighing from 5.7 to 22 kgm., were used. The animals were starved for 30 hours. Eleven dogs were given water ad libitum. The 15 "dehydrated" dogs were deprived of water for 18 to 30 hours and, in the cooler weather, were exercised for 30 minutes the day before the experiment.

Blood pressures were recorded with the glass capsule manometer (6), which gives a fairly good indication of pulse pressure. Heparin was used as the anticoagulant. The following determinations were performed in duplicate: circulating time by the sodium cyanide method (7); *thiocyanate dilution* by the method of Crandall and Anderson (8); plasma volume by the "direct" dye method (9), using the spectrophotometer, calibrated syringes and washing out the syringes with blood after dye injections; plasma protein determinations by the micro-Kjehldal method of Ma (10); non-protein nitrogen by direct Nesslerization (11); arterial CO₂ by the manometric method of Van Slyke and Neill; hematocrits with Wintrobe tubes, centrifuged for one hour at 2,500 R.P.M.; hemoglobins with a photoelectric hemoglobinometer; and red cell counts in the usual manner. Blood samples were taken after draining the stagnant blood from the cannulas.

The experimental procedure was as follows: Under local (procaine) anesthesia, the right femoral and right carotid arteries were cannulated and the left femoral and the right external jugular veins were exposed. A control (arterial) blood sample of 15 to 20 cc. was drawn, and sodium thiocyanate solution was injected intravenously. Then, carotid arterial blood pressure and circulating time were recorded. Forty-four minutes after the injection of the thiocyanate, the blue dye was injected. Sixteen minutes later, the first dye sample was drawn from the femoral artery, and, at 4 or 5 minute intervals, 3 or more successive samples were drawn. Hematocrit determinations were made on alternate dye samples. Immediately after the last sample was drawn, the animal was bled a total of 20 to 30 per cent of its estimated blood volume in a 10 minute period. Blood volumes were calculated as $\frac{1}{13}$ of body weight. Carotid blood pressures were recorded during the bleeding periods. Then the arteries were clamped and the animal was placed on the floor, restrained only by a leash. After about thirty minutes the compensation to the hemorrhage was assumed to be complete (12), and the animal was bled an additional 10 to 15 per cent of its estimated blood volume in a 10 minute period. In this and in all successive bleedings if the mean arterial pressure fell below 45 to 50 mm. of Hg, the bleeding was stopped and the animal removed from the board; thirty minutes later, a third bleeding was performed if the animal's condition permitted it.

Circulatory collapse from hemorrhage or trauma was generally characterized by a persistent fall in the blood pressure to less than 70 mm. Hg, by a progressive increase in the circulating time to 20 seconds or more, and by a decrease in the arterial carbon dioxide content to less than 26 volumes per cent. In this investigation, an animal was considered to be in shock only when at least two of these three criteria were present. Generally, the changes in all three were parallel but, not infrequently, one would give more or less normal values when the other two gave a more accurate picture of the animal's critical condition.

After an average period of 35 minutes following the final hemorrhage, the animals were in shock; a 15 cc. sample of blood was drawn for the various determinations and the dye was injected for the second plasma volume determination. All of the animals died some time after the final hemorrhage unless serum or plasma infusions were administered.

RESULTS. The experiments are divided into two main groups, "non-dehydrated" and "dehydrated" animals.

TABLE 1
Average values for all experiments

	NON-DEHYDRATED ANIMALS		DEHYDRATED ANIMALS	
	Hemodiluting	Hemoconcentrating	Hemodiluting	Hemoconcentrating
No. of dogs.....	9	2	7	8
Wt. (kgm.).....	14.7	8.2	10.7	10.2
"Extra-cellular" fluid (cc./kgm.)	256	253	227	227
Plasma volume (cc./kgm.)	36.0	42.0	36.4	38.5
Circulating blood volume (cc./kgm.) ..	73.6	79.4	74.3	75.3
Total hemorr.				
Cc./kgm.....	36.0	35.7	32.2	32.0
% of control blood volume	49.0	44.9	43.3	42.5

	TIME OF DETERMINATION							
	Control	Post-hemorr.	Control	Post-hemorr.	Control	Post-hemorr.	Control	Post-hemorr.
Hematocrit.....	51.6	43.3	50.2	54.6	50.7	45.2	48.9	53.5
Hemoglobin (grams %)	18.1	14.7	17.5	19.3	17.5	15.4	16.2	17.8
Erythrocyte count (10 ⁶ /mm. ³).....	7.8	6.4	6.9	7.6	7.1	6.0	6.6	7.5
Mean blood pressure (mm. Hg).....	148	58	121	47	126	51	140	48
Circulating time (seconds)..	10.4	38.5	14.5	32.0	9.0	42.3	9.6	39.5
Arterial CO ₂ (vol. %).....	46.4	15.7	39.0	5.1	44.2	17.9	46.6	16.8
NPN (mgm. %).....	32	44	47	62	41	59	40	60
Plasma protein (grams %)..	5.8	4.7	6.3	5.2	6.1	5.0	6.7	5.9

Hemoconcentration occurred in 2 of the 11 "non-dehydrated" and in 8 of the 15 "dehydrated" animals, the average increase in hematocrit being 4.4 and 4.6, respectively. The average decrease in hematocrit for the 7 dehydrated hemodiluting animals was 5.5, whereas in the 9 non-dehydrated hemodiluting animals it was 8.3. The changes in hemoglobin and red cell counts were in the same direction.

The total blood loss which led to shock differed significantly in the various groups. By total blood loss is meant all measured blood lost in hemorrhages, samples, washing out cannulas, etc. The non-dehydrated hemodiluting dogs withstood an average withdrawal of nearly 50 per cent of their average control blood volume, whereas both groups of dehydrated dogs and the non-dehydrated

hemoconcentrating dogs tolerated an average loss of only 43 per cent of their average initial blood volume.

The changes in total plasma protein concentration revealed that in the dehydrated hemoconcentrating group the decrease in the concentration of total protein, after hemorrhage, was significantly less than in the other groups.

An increase in non-protein nitrogen concentration was observed in every animal except in one of the hemodiluting, non-dehydrated group. The greatest increase (50 per cent) was found in the group of dehydrated hemoconcentrating animals.

Average mean blood pressures, 30 minutes after the last hemorrhage, were at shock levels in all groups. Significantly, the blood pressures were highest in the non-dehydrated, hemodiluting animals, although this group had been subjected to the severest hemorrhage (nearly 50 per cent of the average initial blood volume). Pulse pressures were greatly reduced, indicating decreased cardiac output and depleted circulating volume. The importance of low pulse pressures in the diagnosis of shock has recently been given new emphasis (13).

Arterial blood CO₂ content was decreased to very low levels in the animals of all groups.

Circulating time was markedly increased in every animal.

The general condition of the animals when shock was present appeared to be the same in all four groups. It seemed impossible to differentiate dehydrated from non-dehydrated or hemodiluting from hemoconcentrating dogs. All the animals in shock were listless, not responsive to stimuli, and unable to walk. Severe diarrhea occurred in a number of animals of each group and, often, was bloody. In animals in this condition, withdrawing a 10–15 cc. blood sample frequently induced a terminal circulatory collapse within a few minutes. In several such cases, infusion of 5 per cent dextrose in lactate Ringer's solution, in amounts greater than the total volume of blood lost, was attempted but failed to restore the circulation and death soon occurred.

"Extra-cellular" fluid volumes, as measured by thiocyanate dilution, varied too much in the individual dog to permit correlations to be made. It is interesting to note that, despite great individual variations in both groups, the average value for the dehydrated animals was 227 cc./kgm., whereas the average value for the non-dehydrated animals was 255 cc./kgm., both values at the lower range of the normal limits of 230 to 425 cc. per kgm. (14).

Plasma volume values before hemorrhage in all of the animals fell within usual normal ranges (14). We have confirmed the findings of others (15, 16) that plasma volumes, measured by the blue dye, not only give a good index of the clinical condition of the animal, but also correlate well with the other determinations (v.s.) and thus seem to be a reliable measure of the intravascular plasma volume in shock animals. However, because of the uneven distribution of red cells in the circulation and of the unknown amounts of non-circulating red cells, calculated total red cell volumes and total blood volumes are very inaccurate (2, 17) and, consequently, are quantitatively not significant.

In table 2 a comparison of the average percent change in the plasma volume after hemorrhage with the average percent of the control blood volume which

was withdrawn during the period between the first and the second plasma volume determinations indicates that the animals which hemoconcentrated apparently lost plasma fluid and plasma protein in addition to that removed in the hemorrhage, whereas the animals which hemodiluted apparently drew protein-poor fluid into the circulation, during and after the hemorrhage, and had retained it at the time the second plasma volume was determined. The apparent change in circulating red cell volume, and, consequently, the change in total blood volume are less significant for the reasons mentioned above. The validity and interpretation of the apparent loss of additional red cells by the hemodiluting animals and the relative gain in red cells in the hemoconcentrating animals are not established, as yet.

TABLE 2

Average volumes for experiments in which post-hemorrhage plasma volumes were determined

	NON-DEHYDRATED		DEHYDRATED	
	Hemodiluting	Hemoconcentrating	Hemodiluting	Hemoconcentrating
No. of dogs.....	5	1	5	5
Hemorr. between control and post-hemorrhage plasma volume determinations				
Cc./kgm.....	29.3	36.0	28.8	29.3
% of control blood volume.....	39.8	39.8	36.8	38.2

	CONTROL	POST HEM.	% DECREASE	CONTROL	POST HEM.	% DECREASE	CONTROL	POST HEM.	% DECREASE	CONTROL	POST HEM.	% DECREASE
Plasma volume (cc./kgm.)	36.0	26.2	27.2	45.1	24.4	46	37.5	26.4	29.5	41.0	23.8	42.6
Circulating blood volume (cc./kgm.)	74.0	46.1	37.6	90.2	55.7	39.3	78.3	51.7	34.0	76.8	47.0	38.8
Total circulating protein (grams/kgm.)	1.9	1.13	40.5	2.57	1.0	61.1	2.43	1.54	37.0	2.59	1.21	54

Pathological findings were variable, as others (13) have reported. Only 11 animals which did not receive infusions will be considered. The gross findings were not consistent in all cases of each group. Generally, the gut was moist, flabby and atonic, and the lumen often contained gross blood. The intestinal mucosa often was engorged and hemorrhagic throughout. The peritoneal and pleural cavities rarely contained increased amounts of free fluid, and, in only one case, was this blood-stained. The lungs, in some dogs, were engorged and moist but, generally, they presented a fairly normal gross appearance. Nothing of significance was found on gross inspection of the other viscera. The outstanding microscopic findings were focal congestion and engorgement of the lungs, marked engorgement and central necrosis in the liver, marked engorgement of the zona fasciculata of the adrenals, and marked engorgement of the intestine and kidney.

DISCUSSION. Hemoconcentration, as measured by hematocrit, red cell count, hemoglobin, etc., has been advanced as a *sine qua non* of shock. Starting from the premise that hemorrhage is followed by hemodilution, Moon (1) has warned investigators not to apply incorrectly to "true" shock conclusions drawn from animals subjected to hemorrhage. Our results differ markedly from his in certain important respects, for by uncomplicated graded hemorrhage we have produced all of the symptoms and most of the important signs which he contends appear only in "true" shock. Moreover, these findings were observed in a number of animals long before death and in others which survived after serum or plasma infusions, and, therefore, cannot be dismissed as pre-terminal phenomena. That hemoconcentration appeared in more animals of the dehydrated group does not affect the conclusion that the oligemia produced by severe hemorrhage, alone, may be sufficient to produce shock.

Adolph (12) has demonstrated that it is unreliable to use the changes in the peripheral blood red cell concentration as estimations of loss or gain of fluid from the circulation, since stored red cells can be shifted rapidly into or out of active circulation. Thus, an apparent hemoconcentration may mean not a loss of plasma but a gain of cells by the circulating blood. However, with T-1824, plasma volumes can be determined fairly accurately and, by a comparison of the observed plasma volume after hemorrhage with the expected plasma volume, calculated by subtracting from the initial plasma volume the amount of plasma removed in hemorrhage, quantitative estimations of fluid shifts can be derived. In 37 anesthetized dogs which hemodiluted after prolonged bleeding, Price (2) reported a significant average gain of fluid. Similar calculations led us to the conclusion that our dogs which hemoconcentrated actually lost fluid from the blood stream in addition to that lost by hemorrhage, whereas the hemodiluting animals tended to retain fluid gained after the hemorrhage. From this it is clear, therefore, that the hemoconcentration which we observed in a number of dogs was due to the loss of additional fluid from the circulation after hemorrhage.

From the total circulating protein before and after hemorrhage (table 2) and the amount of protein removed in bleeding, it can be calculated that the animals which lost fluid actually lost protein from the circulation, too. If allowance is made for this protein loss, the decrease in plasma protein concentration after hemorrhage in the hemoconcentrating animals indicates that initially, like the hemodiluting animals, these animals must have drawn a relatively protein-poor fluid into the circulation. Thus the total fluid ultimately lost, after the animals began to hemoconcentrate, actually must have been greater than the amounts calculated.

These changes in plasma protein concentration also indicate that the dehydrated hemoconcentrating animals could hemodilute less than all the others. Calvin (18) has shown that, in response to moderate hemorrhage, dehydrated dogs can hemodilute less than normal ones. This possibly explains the inability of our dehydrated animals to tolerate as much bleeding as the hydrated animals before going into shock. This, also, may have decreased the masking effect of the earlier hemodilution upon the later outpouring of fluid from the circulation as shock develops and progresses.

One important question remains: why did 2 of the 11 non-dehydrated dogs display hemoconcentration and why did only 8 of the 15 dehydrated dogs display hemoconcentration? This may be part of the broader problem of why some investigators have been able to observe hemoconcentration following hemorrhage and others not. Blalock (3) and Harkins (4) have stressed the possibility that this discrepancy may depend on the time factor, stating that sufficient time must elapse after hemorrhage before hemoconcentration can occur. But whether hemoconcentration will occur after hemorrhage may depend as much, or even more, on the state of hydration of the animal and on the physiological and pathological variables which affect hydration. A supposedly "normal," non-dehydrated animal actually may be dehydrated and in poorer condition than a healthy young animal that has been dehydrated experimentally for 30 hours. Until more accurate means of determining intra-cellular and extra-cellular water are developed, the evaluation of the factor of hydration in an individual case will be difficult. Our group averages for "extra-cellular" fluids (i.e., thiocyanate dilution) point in that direction, however.

Under the stress of modern warfare, dehydration of combatants may occur and severe hemorrhage may produce shock with hemoconcentration. It would seem to be unwise, therefore, to differentiate hemorrhagic shock from shock produced by other causes. Further, our studies indicate that the appearance of hemoconcentration following hemorrhage is a *signum male ominis*. The clinician who believes that only hemodilution can follow hemorrhage, in the absence of hemodilution, may have a false sense of security in the belief that the patient has not lost much blood. The opposite may actually be the case. In most instances, fortunately, the prevailing clinical picture will give adequate warning of the patient's critical condition.

SUMMARY

1. Typical shock has been produced by graded hemorrhage in 11 non-dehydrated, and in 15 dehydrated, unanesthetized, normal dogs.

2. In 2 of the non-dehydrated (18 per cent) and in 8 of the dehydrated animals (53 per cent), hemoconcentration occurred. Plasma volume and plasma protein determinations, before and after hemorrhage, revealed that the animals which hemoconcentrated, actually lost additional plasma fluid and protein as shock developed.

3. Pathologic changes consisting of gastro-intestinal engorgement and hemorrhage, pulmonary congestion and engorgement, and occasional changes in other viscera were observed in a number of animals.

4. The hemodiluting, non-dehydrated animals tolerated an average total blood loss of 49 per cent as compared to an average total blood loss of 43 per cent tolerated by the other animals.

5. The changes in plasma protein concentration after hemorrhage indicated that the hemoconcentrating dehydrated animals hemodiluted during and after hemorrhage to a lesser degree than the other 3 groups. This relative inability to hemodilute could explain their inability to tolerate as much bleeding

before going into shock and could lessen the masking by earlier hemodilution of the subsequent hemoconcentration as shock develops.

6. It is suggested that the conflicting reports as to the occurrence of hemoconcentration after hemorrhage may be related to the state of hydration of the animals studied.

7. It is concluded that there are no definite grounds for differentiating between hemorrhagic shock and shock from other causes.

REFERENCES

- (1) MOON, V. H., D. R. MORGAN, M. M. LIEBER AND D. MCGREW. *J. A. M. A.* **117**: 2024, 1941.
- (2) PRICE, P. B., C. R. HANLON, W. P. LONGMIRE AND W. METCALF. *Bull. Johns Hopkins Hosp.* **69**: 327, 1941.
- (3) BLALOCK, A. *Principles of surgical care; shock and other problems.* C. V. Mosby Company, St. Louis, 1940.
- (4) HARKINS, H. N. *Surgery* **9**: 231, 1941.
- (5) LEVINSON, S. O., F. NEUWELT AND H. NECHELES. *J. A. M. A.* **114**: 455, 1940.
- (6) ANDERSON, F. F. *J. Lab. and Clin. Med.* **26**: 1521, 1941.
- (7) OLSON, W. H., H. GUTMANN, S. O. LEVINSON AND H. NECHELES. *War Med.* **1**: 830, 1942.
- (8) CRANDALL, L. A., JR. AND M. X. ANDERSON. *Am. J. Digest. Dis. and Nutrition* **1**: 126, 1934.
- (9) GIBSON, J. G. AND W. A. EVANS, JR. *J. Clin. Investigation* **17**: 153, 1938.
- (10) MA, T. S. AND G. ZUAZAGA. *Indust. and Eng. Chem., Analytical Edition* **14**: 280, 1942.
- (11) FOLIN, O. AND W. DENIS. *J. Biol. Chem.* **26**: 473, 1916.
- (12) ADOLPH, E. F., M. J. GERBASI AND M. J. LAPORE. *This Journal* **104**: 502, 1933.
- (13) WIGGERS, C. J. *Physiol. Rev.* **22**: 74, 1942.
- (14) GREGERSEN, M. J. AND J. D. STEWART. *This Journal* **125**: 142, 1939.
- (15) GREGERSEN, M. J. Personal communication.
- (16) GIBSON, J. G., II. Personal communication.
- (17) STEAD, E. A., JR. AND R. V. EBERT. *This Journal* **132**: 411, 1941.
- (18) CALVIN, D. B. *J. Lab. and Clin. Med.* **26**: 1144, 1941.

